

**REMARKS**

Claims 1-11 and 25-34 presently appear in this case. No claims have yet been examined on the merits. All of the claims have been subject to a restriction requirement. The official action of February 13, 2006, has now been carefully studied. Reconsideration and withdrawal of this restriction requirement and examination and allowance of all of the claims presently appearing in the case are respectfully urged.

The Examiner has required restriction among the following groups:

Group I, including claims 1-6, drawn to a method for inhibiting aggregation of  $\beta$ -amyloid in a subject;

Group II, including claims 7-11, drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier, and a filamentous bacteriophage that displays a  $\beta$ -amyloid antibody or epitope;

Group III, including claims 12-18, drawn to a method for inhibiting aggregation of a prion protein in a subject; and

Group IV, including claims 19-24, drawn to an antibody that binds a prion protein.

This restriction requirement is respectfully traversed.

In order to be responsive, applicants hereby elect Group II, i.e., the pharmaceutical composition claims including claims 7-11. It is urged, however, that the method of use claims 1-6 should be examined with the composition

claims for the same reasons that a similar restriction requirement was withdrawn in parent application no. 10/162,889, and that both groups were examined together in grandparent application 09/629,971 and in great-grandparent application 09/473,653. Furthermore, if the composition is found to be allowable over the prior art, then the method of use of the composition should also be allowable over the prior art. Accordingly, it is at least requested that the claims to the method of use only be temporarily withdrawn from reconsideration but be rejoined in accordance with MPEP §821.04 once the composition claims are found to be allowable. Claims 12-24 from non-elected Groups III and IV have now been deleted without prejudice toward the continuation of prosecution thereof in a continuing application.

The examiner has further required an election of species among:

- (a) SEQ ID NO:7
- (b) SEQ ID NO:8
- (c) SEQ ID NO:21
- (d) SEQ ID NO:22

The examiner stated that if applicants elect invention I or II, one species from the epitope groups (a)-(d) must be chosen to be fully responsive. The examiner concedes that claim 1 is currently generic and that upon allowance of a generic claim, applicants will be entitled to consideration of claims to additional species that are written in dependent form or otherwise include all of the limitations of the

allowed generic claim. The examiner requires a listing of all claims readable on the elected species.

It is not understood why the examiner has not included SEQ ID NO:1 (claim 8) as one of the possible species. This was listed as one of the species in the restriction requirement in parent application 10/162,889. If this was an oversight on the part of the examiner, it is requested that the list of species be corrected and applicant be permitted to elect SEQ ID NO:1. If the examiner refuses to accept the election of SEQ ID NO:1, applicant elects SEQ ID NO: 7 in order to be responsive.

Regardless of whether SEQ ID NO: 1 or SEQ ID NO: 7 is considered to be the elected embodiment, all of elected claims 7-11 read on the elected embodiment, as do method claims 1-6. New claims 25-34 have now been added and will be discussed below. It is believed that all of these claims are drawn to the same invention as elected Group II and that all of them read on the elected embodiment.

Reconsideration of the restriction requirement to the extent requested above and allowance of all of claims 1-11 and 25-34 in this case are respectfully urged.

In the Office action of July 2, 2003, in parent application 10/162,889, all of the claims were rejected. The following is responsive to that Office action.

In the Office action of July 2, 2003, in parent application 10/162,889, the method-of-use claims (which correspond to present claims 1-6) were rejected under 35

U.S.C. §112, first paragraph, because the specification, while being enabling for an *in vitro* method of inhibiting aggregation of  $\beta$ -amyloid comprising contacting a cell line expressing  $\beta$ -amyloid with a filamentous bacteriophage which displays an antibody or epitope binding fragment thereof, wherein said antibody and epitope binding fragment thereof binds to an epitope of  $\beta$ -amyloid wherein the epitope of  $\beta$ -amyloid comprises the amino acid sequence of SEQ ID NO:1, or wherein said epitope is contained in a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:21 and SEQ ID NO:22, does not reasonably provide enablement for a method of inhibiting aggregation of  $\beta$ -amyloid in a subject or disaggregating aggregated  $\beta$ -amyloid in a subject comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition of the aforementioned filamentous bacteriophage. The examiner stated that the specification does not enable any person skilled in the art to use the invention commensurate in scope with these claims. The examiner stated that none of the examples provides sufficient guidance that would lead to the inhibition and/or disaggregation of  $\beta$ -amyloid in a patient with Alzheimer's disease. The examiner stated that, absent a nexus between the claimed phage and a salubrious effect thereof in Alzheimer's patients or an animal model, a therapeutic treatment is unpredictable and would require an undue amount of experimentation in view of the unpredictable degree of success

to practice the claimed invention. Further, the examiner stated that the specification provides no guidance on how to prevent Alzheimer's disease. The examiner stated that, in order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of dosages, evaluation of effectiveness, and possibly new diagnosis methods as the only current method of examining  $\beta$ -amyloid plaques involves immunocytochemistry. This rejection is respectfully traversed.

First of all, it is pointed out that none of the present claims specifically mention "Alzheimer's disease". It is not understood why the examiner believes that, in order for the claimed method to be carried out, a salubrious effect on Alzheimer's patients must be established or some alleviation of a symptom associated with Alzheimer's disease must be established. Such is not required by the claims. All that is required is that the aggregation of  $\beta$ -amyloid be inhibited or slowed, or that there be some disaggregation of aggregated  $\beta$ -amyloid. There is no reference to Alzheimer's disease anywhere in the claims. If a person has aggregating  $\beta$ -amyloid, and this aggregation is slowed, that, in itself, is a sufficient utility, as it is known that aggregation of  $\beta$ -amyloid has pathogenic effects. Similarly, if plaque can be disaggregated in any amount, this is to be desired, whether or not it alleviates a symptom associated with Alzheimer's

disease. The technique of the present invention may be used for its additive effect with other Alzheimer's treatment to achieve appropriate salubrious effects in Alzheimer's patients, but the mere fact that aggregation of  $\beta$ -amyloid is being slowed or that disaggregation occurs in any amount is sufficient utility in and of itself and is all that is required by the present claims.

The examiner stated that resolution of the various complications in Alzheimer's disease therapy makes the art highly unpredictable. However, applicants are not claiming a treatment of Alzheimer's disease. The present claims only require that the aggregation of  $\beta$ -amyloid in a subject be inhibited or aggregated  $\beta$ -amyloid in a subject be disaggregated in any amount. Such a claim is similar to processes directed to AIDS patients drawn to a therapy that reduces viral load. Reducing the viral load of HIV may not necessarily establish any improvement of symptoms in AIDS patients, but it is certainly a desirable therapeutic effect. Similarly here, slowing or reversal of aggregation in any amount is desirable, and any Alzheimer's patient or patient with incipient Alzheimer's would be better off with such a slowing or even with a small amount of disaggregation than without the treatment, regardless of whether any symptom is being treated.

The examiner also stated that the examples do not show prevention since fibrils are formed in all the samples. However, none of the present claims require prevention.

Inhibition of aggregation is not the same as prevention. It only means that the aggregation is slowed, not necessarily prevented. We note that the examiner stated in the first sentence of paragraph 18 that "the instant specification provides ample evidence that the claimed bacteriophage construct may slow or inhibit amyloid formation *in vitro*."

With these understandings, there is no cause to doubt the claimed *in vivo* activity. Accordingly, dosages can be established in a conventional manner without resorting to undue experimentation. A diagnostic method is not being claimed nor is one required in order to practice the present invention.

Notwithstanding the above, experiments have now been conducted that establish the ability of the phage displayed antibodies or antibody fragments of the present invention to inhibit  $\beta$ -amyloid aggregation and/or disaggregate  $\beta$ -amyloid aggregation in an accepted mouse model of Alzheimer's disease. The examiner's attention is invited to the attached declarations of Dr. Beka Solomon and Dr. Birgit Hutter-Paier, which detail these experiments and the experimental results. The hAPP751-transgenic mice were used in these experiments. It is known from papers, such as Higgins et al, "Early Alzheimer's disease-like histopathology increases in frequency with age in mice transgenic for  $\beta$ -APP751," PNAS USA 92:4402-4406 (1995), a copy of which is attached to Dr. Solomon's declaration, that these mice show age-related  $\beta$ -amyloid deposition.

In the experiments reported in the attached declarations, it can be seen that intranasal treatment of the mice with filamentous bacteriophage displaying scFv508 resulted in four of the ten treated mice being totally devoid of amyloid aggregation, four showing a reduction between 60% and 80%, while only two showing little effect on  $\beta$ -amyloid aggregation. Brain tissues from mice which contained no amyloid deposits proved positive for their hAPP gene existence after re-examination. The mice in the control group contained amyloid deposit load values ranging from 1.05% to 2.8%. Overall, the treatment resulted in a reduction of about 70% in amyloid deposit load compared to the transgenic untreated animals. The olfactory bulbs were the most affected areas in treated mice, exhibiting an average of 90% reduction in amyloid deposit load.

This evidence, particularly the 40% of the treated mice that are totally devoid of amyloid aggregation, establishes in an *in vivo* model that the results expected from the *in vitro* tests are, indeed, obtained in the *in vivo* model. There is substantially less deposition than in the control mice. The fact that substantially no deposition appeared in 40% of the mice indicates not only that aggregation was inhibited, but that disaggregation took place. Accordingly, while it is not believed that any *in vivo* data is necessary to establish enablement for the present invention for the reasons discussed above, nevertheless, the experimental results

detailed in the attached declarations prove the enabling nature of the present specification.

It is noted that the examiner referred to Pan et al, "Antibodies to  $\beta$ -amyloid decrease the blood-to-brain transfer of  $\beta$ -amyloid peptide," Exp Biol Med 227:609-615 (2002) and concedes that it teaches that the administration of anti- $\beta$ -amyloid antibodies to PDAPP mice decreases the incidence of  $\beta$ -amyloid plaques, not through disaggregation, but through decreasing the concentration of  $\beta$ -amyloid in the central nervous system. Thus, the examiner stated that the  $\beta$ -amyloids are not disassembled or prevented *per se*, but their formation is inhibited or, in another sense, slowed.

It should be noted that Pan is not available as prior art, but, far from supporting the examiner's rejection, actually supports enablement of the present invention. The present claims do not require prevention or disassembly of  $\beta$ -amyloid aggregates. The claims only require either inhibition of aggregation of  $\beta$ -amyloid or disaggregation of aggregated  $\beta$ -amyloid in a subject. The claims do not require both. The reduction in the amount of plaque that would otherwise be present without treatment is what is important, whether this is caused by inhibition of aggregation or by disaggregation. Pan confirms that amyloid aggregate formation is inhibited or slowed by the administration of anti- $\beta$ -amyloid antibodies to PDAPP mice. Accordingly, there is no reason to disbelieve applicants' statement that such antibodies presented on phage will inhibit aggregation.

The examiner conceded that the specification provides ample evidence that the claimed bacteriophage construct may slow or inhibit amyloid formation *in vitro*, but the examiner stated that the specification does not provide any evidence of disassembly or disaggregation, both of which are active processes. However, the claims do not require disassembly or disaggregation. They require either inhibition or disaggregation. It does matter which of these two mechanisms or both lead to the end result of having less plaque after treatment than would have been present had there been no treatment. Furthermore, as discussed above, the attached *in vivo* data suggests that in at least 40% of the mice tested, some disaggregation must have occurred.

The examiner stated that the concept of an active destruction of existing amyloid fibrils is contrary to the prior art. However, this is not the case. As reported in the present specification in paragraph [0015], antibodies against the EFRH epitope have been shown to disaggregate  $\beta$ -amyloid fibrils. The Solomon (1997) reference cited in that paragraph and of record in this case as reference CR clearly shows disaggregation of Alzheimer  $\beta$ -amyloid by site-directed monoclonal antibodies.

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

In the Office action of July 2, 2003, in parent application 10/162,889, the pharmaceutical composition claims (which correspond to present claims 7-11) were rejected under

35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The examiner stated that none of the examples in the present specification provides sufficient guidance that would lead to the inhibition and/or disaggregation of  $\beta$ -amyloid in a patient with Alzheimer's disease. The examiner stated that the specification fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* application of the method as exemplified in the references discussed in the enablement rejection of the method-of-use claims. It is noted that the examiner specifically indicated that this rejection of the composition claims would be obviated by removal of "pharmaceutical" from the claims. This rejection is respectfully traversed.

The reasons for this rejection are substantially the same as the reasons for the rejection of the method-of-use claims. As the enablement rejection of the method-of-use claims has been shown to be untenable hereinabove, the present rejection should be withdrawn for the same reasons as discussed hereinabove with respect to the method-of-use claims.

With respect to the examiner's suggestion that the rejection of the composition claims would be obviated by removal of "pharmaceutical," new claims 25-34 have now been added. Claims 25-29 adopt the examiner's suggestion and delete reference to "pharmaceutical" or "pharmaceutically

acceptable" in the claims. Furthermore, claims 25-34 have been amended so as not to recite that the aggregation must necessarily occur "in a subject." As the examiner has agreed that the rejection is obviated for such claims, it is urged that at least claims 25-29 must now be in condition for allowance.

New claims 30-34 are directed to the same filamentous bacteriophage that is claimed in claim 24 with the addition of a carrier. However, claims 30-34 are directed to the bacteriophage *per se* and not to a composition containing that bacteriophage on a carrier. These claims should be allowable for the reasons that the examiner has indicated that claims 25-29 would be allowable.

Accordingly, reconsideration and withdrawal of this rejection and allowance of all of claims 7-11 and 25-34 are respectfully urged.

It is requested that the examiner initial all of the forms PTO/SB/08A and 08B that have been submitted with Information Disclosure Statements in the present application and return them to applicants to establish that these documents have been considered and that they will be of record on the face of any patent that issues from the present application.

It is submitted that all of the claims now present in the case fully comply with 35 U.S.C. §112 and fully define over the references of record. Reconsideration and allowance are, therefore, earnestly solicited.

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Respectfully submitted,

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